Journal of Hematopathology (2019) 12:51–56
https://doi.org/10.1007/s12308-019-00352-0

ORIGINAL ARTICLE

Human endogenous retrovirus, HERV-P and HERV-R in pediatric leukemia patients

Massimiliano Bergallo[1] · Katia Mareschi[1,2] · Paola Montanari[1] · Cristina Calvi[1] · Massimo Berger[2] · Ilaria Bini[2] · Valentina Daprà[1] · Ilaria Galliano[1] · Franca Fagioli[1,2]

Received: 5 December 2018 / Accepted: 2 April 2019 / Published online: 3 May 2019

Abstract

The "HERVs" (human endogenous retroviruses) are a family of endogenous retroviruses integrated into the germ cell DNA of primate over than 30 million years ago. HERV expression seems impaired in several diseases, ranging from autoimmune to neoplastic disorders. The purpose of this study was to evaluate the overall endogenous retroviral transcription profile in bone marrow (BM) samples. A total of 30 pediatric lymphoid and myeloid malignancies patients were tested. Our findings show that HERV-R expression results significantly higher in leukemia patients than donors. This overexpression might be related to lymphatic leukemogenesis and it warrants further investigations.

Keywords HERVs · Leukemia · Lymphoblastic leukemia (ALL) · Acute myeloid leukemia (AML) · Chronic myeloid leukemia (CML) · Juvenile myelomonocytic leukemia (JMML)

Introduction

The human endogenous retroviruses (HERVs) are composed of many families of endogenous retroviruses that were integrated into the germ DNA of the primate line over the last ~30 million years [1]. Currently, HERVs are classified into 50–200 families depending on the primer binding site (PBS) sequences complementary to the 3′ end of a cellular tRNA used for reverse transcription [2, 3]. However, transcription of HERV elements is usually suppressed by epigenetic factors such as DNA methylation and heterochromatin silencing by histone adjustments; inserted LTRs act as alternative promoters to stimulate expression of adjacent genes causing the activation of oncogenes or inactivation of tumor suppressor genes [4, 5]. The re-activation of HERV transcription as a consequent to various factors (such as radiations, chemicals, other exogenous viral infections) could act as a promoter for the development of several malignancies through the modification in cell gene expression [6–8]. There are only few studies on the expression of endogenous retroviruses in pediatric leukemias [9–12]; moreover, data regarding the participation of HERV-K and W in the development of leukemia are contradictory [12–14]. One study compared the mRNA expression of HERVs in tumors to adjacent normal tissues and found high levels of HERV-K expression in testis tumor tissues, HERV-R (ERV3–1) in liver and lung tumor tissues; HERV-H in liver, lung, and testis tumor tissues; and HERV-P in colon and liver tumor tissues [13]. Specifically during hemato-oncological processes, several studies have reported overexpression of HERV genes and also the presence of retroviral particles in primary leukemia cells [15].

These considerations led us to study *pol* gene expression of HERV-P and HERV-R in bone marrow (BM) samples from a cohort of consecutive pediatric patients with leukemia. We expect that the results obtained will be able to provide some insight into the role of endogenous retroviruses in the pathogenesis of leukemia.

Material and methods

Patients and samples

BM cells were collected from 30 leukemia pediatric patients as reported in the Table 1 and from 20 pediatric healthy subjects with similar median age.

✉ Massimiliano Bergallo
Massimiliano.bergallo@unito.it

[1] Department of Public Health and Pediatric Sciences, University of Turin, Medical School, 10126 Turin, Italy

[2] Pediatric Onco-Hematology and Stem Cell Transplantation and Cell Therapy Division, City of Science and Health of Turin, Turin, Italy

BM mononuclear cells were separated, total RNA extracted and reverse-transcribed as previously reported and [12]. All analyzed samples were BM cells which were collected from BM aspirates in the patients at the moment of the diagnosis and from BM collection in the pediatric related donors.

The study was conducted in accordance with Declaration of Helsinki for experiments involving humans, and informed consent was obtained in each case from the parents or their legal guardians.

Relative quantification by real-time PCR

Relative quantification of mRNA expression of *pol* genes was achieved by means of Taqman amplification and normalization to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which was chosen as a reference gene, using the ABI PRISM 7500 real-time system (Life Technologies, TX, USA). Approximately 100 ng cDNA were amplified in a 20 μl total volume reaction containing 2× GoTaq® Probe qPCR Master Mix (Promega, Madison, WI, USA), and 900 nmol of specific HERV-P primers (HERV-PF-5′-CAGG GTCCTCTCAAACCCTGT-3′) (HERV-PR-5′-TGGG TCAGCAAGGTATAGCGA-3′) and probe (HERV-P-6FAM-TGCGGCCAAAGTCCCAATCCATCCAGT-TAMRA) or HERV-R primers (HERV-RF-5′-GCAC GAGTCAGCGGTGAAGA-3′) (HERV-RR-5′-GGGC TCAGGCAATTTCTGGT-3′) and probe (HERV-R-6FAM-CGGACCCGCTCAACCCAACAGTTCCG-TAMRA) or GAPDH specific primers [12]. The amplifications were in a 96-well plate at 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1 min. Each experiment was repeated in triplicate.

Table 1 Clinical data of patients entering in the study

Pt	Diagnosis	Gender	Age at diagnosis	BM blasts (%)
1	AML M0, FLT3-ITD	F	15 years	85
2	AML M4, FLT3-ITD	M	7 years	69
3	AML M5, no mutations	F	3 years	47
4	CML, BCR/ABL p210	F	12 years	5
5	AML M4, t(8;16)	M	7 months	21
6	ALL common, BCR/ABL p210	F	11 years	93
7	ALL common, no mutations	M	11 years	83
8	AML M2, t(6;9)	M	10 years	47
9	AML M4, no mutations	F	7 years	53
10	CML, BCR/ABL p210	F	11 years	8
11	AML M4, MLL/AF6	F	16 years	95
12	AML M2, FLT3-ITD e NPM1+	M	2 years	85
13	ALL common, BCR/ABL p190	F	1 year	88
14	ALL common, no mutations	M	10 years	46
15	ALL common, no mutations	F	7 years	77
16	ALL common, hypodiploid	M	15 years	90
17	CML, BCR/ABL p210	M	13 years	1
18	AML M4, RUNX1-RUNX1T1 and del(9)	M	10 years	58
19	ALL common, BCR/ABL p190	F	16 years	86
20	ALL early T, no mutations	M	8 years	87
21	AML M1, RUNX1-RUNX1T1	M	1 year	90
22	AML M2, MOZ/CBP	M	13 years	92
23	AML M5, t(10;11)	M	5 years	60
24	AML M5, no mutations	M	4 years	62
25	CML, BCR/ABL p210	F	4 years	1
26	ALL common, BCR/ABL p190	M	11 years	44
27	JMML, PTPN11	F	1 year	0.8
28	AML M7, BCR/ABL p210 and *CBFB-MYH11*	M	7 months	85
29	ALL early T, no mutations	M	18 years	85
30	AML M2, FLT-3 ITD	F	17 years	90

F female, M male, BM bone marrow, AML acute myeloid leukemia, ALL acute lymphoblastic leukemia, CML chronic myeloid leukemia, JMML juvenile myelomonocytic leukemia, DOD dead of disease, A&W alive and well, HSCT hematopoietic stem cell transplantation

Statistical analysis

The differences between HERV-P and -R expression were, respectively, evaluated comparing the patients with the donors by unpaired two-tailed Student's *t* test with Welch's correction using the Prism software (GraphPad Software, La Jolla, CA). In all analyses, $p < 0.05$ was taken to indicate a statistical significance between the analyzed groups.

Results

The study group enrolled 30 pediatric leukemia patients (15 acute myeloid leukemia (AML), 10 acute lymphoblastic leukemia (ALL), 4 chronic myeloid leukemia (CML), and 1 juvenile myelomonocytic leukemia (JMML)) diagnosed and treated in our center. Table 1 summarizes the patient's characteristics. The median age of the patients and healthy cohort were 10.3 years, respectively, with a range of 0.8–18.6 and 3.9–16.4 years.

Because retro-transcription efficiency was equivalent in all samples, as suggested by GAPDH expression (data not shown), we made the hypothesis that the strong variations of signal intensity between mononuclear cells from leukemia patients and normal BM cells might be related to differences in HERV-P and -R *pol* transcriptional levels.

Relative expression of HERV-P and HERV-R *pol* gene in leukemia samples vs healthy donor

As shown in the Fig. 1, 9 of 30 samples (30%) showed a higher expression of HERV-P in comparison to healthy donors but the difference was not statistically significance ($p = 0.6014$). Conversely, HERV-R expression resulted significantly higher in the leukemia patients than healthy subjects ($p < 0.0001$). In particular, all samples out of 30 (100%) showed higher HERV-R levels than the average of healthy subjects.

Relative expression of HERV-P and HERV-R *pol* gene analyzing their expression in the different types of leukemia

The comparison of HERV-P expression between the ALL patients and the healthy donors, patients with myeloid malignancies (ML), and healthy donors and ALL and ML patients did not show any significant differences ($p = 0.7226$, 0.3681 and $p = 0.3735$, respectively) as shown in the Fig. 2a–c.

HERV-R expression was higher in the ALL and in ML patients in comparison to the donors, and the differences were both statistically significant ($p < 0.0001$) as shown in the Fig. 2d, e. This significant difference on HERV-R was not observed when we compared ML patients with ALL patients ($p = 0.2810$; Fig. 2f).

Relative expression of HERV-K and HERV-W *pol* gene analyzing their expression in the different types of karyotypes

Then, we analyzed data obtained from the amplification of the *pol* gene of HERV-P and -R in specific subgroups of patients with an altered karyotype. We compared their expression in BCR/ABL, FLT3 mutated patients or showing other translocations (t(6,11),(10,11), (8,16)) with leukemia patients without mutations. We observed a trend of higher expression of HERV-P in the subgroups with an altered karyotype, but without significant statistical differences ($p = 0.4169$ for HERV-P and $p = 0.7468$ for HERV-R, respectively, for the analysis between no mutations and BCR/ABL+, FLT-3+, and other translocations subgroups).

Discussion

The physiological role of HERV is still unknown, even if some HERVs have been found to show organ-specific expression, proposing an association between HERV and the development and differentiation of human tissues [16]. In malignancy, a relationship between HERV family type and histological type has been proposed [13].

The aim of this study was to evaluate the overall endogenous retroviral transcription profile in BM samples of a representative cohort of high-risk leukemia pediatric patients. Our findings show that HERV-R expression resulted higher in leukemia patients (ALL and LM) vs healthy subjects with the same median of age. These findings might suggest that the HERV-R *pol* gene could play a role in the cell proliferation activity. This specific expression in leukemia patients also suggests that HERV-R *pol* gene could be considered as a target for gene therapy.

The number of papers in the literature exploring the role of HERVs in leukemia patients are reduced and show data to be confirmed. In particular, Januszkiewicz-Lewandowska and colleagues observed a high relative expression of the *env* gene in acute ML suggesting a participation of env sequences in the pathogenesis of leukemia [11]. Fischer and colleagues recently presented that only 2 out of 25 chronic lymphocytic leukemia patients exhibited elevated HERV-K *gag* expression (5-fold greater than healthy donors) [15]. Ahn and Kim investigated the HERV expression between the cancer tissues and adjacent normal tissues and observed high levels of HERV-R, -K, P, and -R observed in various cancer tissues compared to the adjacent normal tissues [13]. Otherwise, it must be taken into account that chronic antigen stimulation could also trigger HERV overexpression as a consequence of cytokine production and inflammation [17, 18].

It remains also to ascertain whether the high HERV values we found in leukemia patients are related to the clinical outcome.

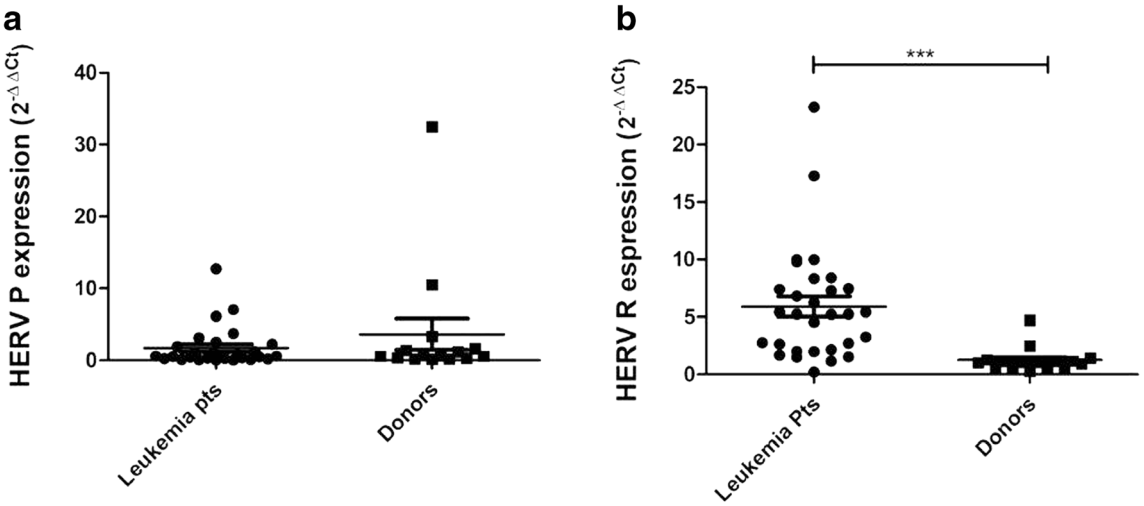

Fig. 1 Expression of the pol gene of HERV-P (**a**) and -R (**b**) evaluated by quantitative PCR real-time in the leukemia patients and the healthy donors expressed as $2^{-\Delta\Delta Ct}$. HERV-R expression resulted higher in the leukemia patients than healthy subjects .The symbol *** indicate a statically significant difference with $p < 0.001$ calculated by Mann-Whitney *U* test for the expression of HERV-R in the leukemia patients in comparison with donors

The transcriptional activation of HERVs is a common feature in many human cancers. RNAs of HERV-K were found in testicular and ovarian germ cell tumors, as well as in gestational trophoblastic disease [19–21]. Indeed, in association to the DNA hypomethylation, an aberrant expression of syncytin-1 (HERV-W) has been found in biopsies from seminoma patients [22]. Remarkably, the expression of env of HERVs such as H, K, R, and P was found high in patients with breast cancer and resulted reduced during chemotherapy [23]. In prostate cancer, HERV-E and HERV-K expression was found in cancer tissue, cell lines, and peripheral mononuclear cells from patients [24]. HERV-K expression was found high in leukemia [9], in childhood acute

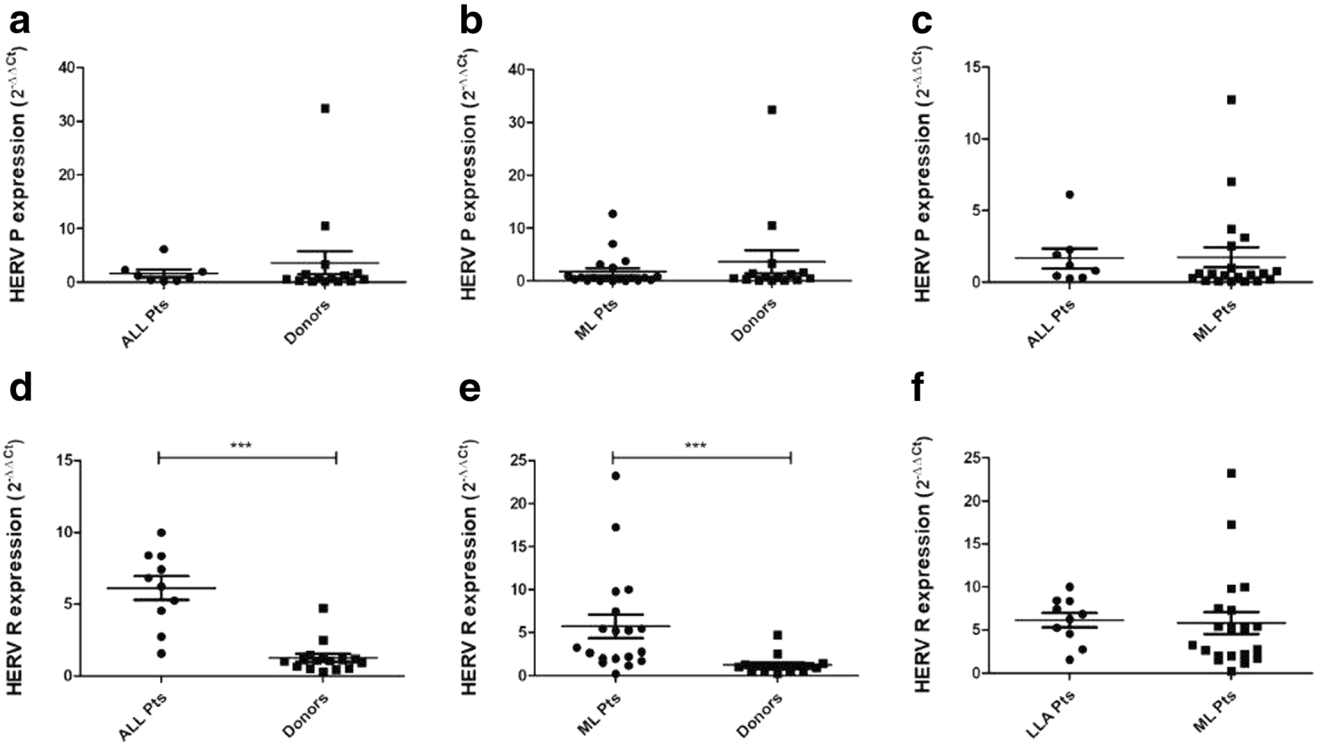

Fig. 2 Expression of the pol gene of HERV-P (**a**–**c**) and -R (**d**–**f**) expression evaluated by quantitative real-time PCR. **a**, **d** Comparison of pol env expression between ALL patients and healthy donor subjects. **b**, **e** Comparison between myeloid malignancy patients and healthy subjects. **c**, **f** Comparison between ALL and myeloid malignancies patients. The symbol *** indicates a statistically significant difference ($p < 0.001$) calculated by an unpaired *t* test with Welch's correction

lymphoblastic leukemia [10], and in pediatric high-risk leukemia patients [12]. In addition, HERV-W transcription levels were found elevated in lesions of the primary cutaneous in T cell lymphomas (CTCLs) [25, 26]. Recently, HERV-H transcripts were found be associated to colon cancer [27, 28]. Recently, HERV-K expression has been associated with soft tissue sarcoma [29] and hepatocellular carcinoma prognosis [30]. Moreover, HERV-K (HML-2) env expression was detected on seven pancreatic cancer cell lines and in 80% of pancreatic cancer biopsies, but not on normal pancreatic cell lines or on normal tissues [31].

To date, a growing body of findings supports the idea that HERVs may be a causative agent or at least a cofactor in carcinogenesis. Given to the potential ability to retrotransposon [32], it is the belief that HERV tumorigenicity could depend on retroviruses movement and consequently in de novo formation of proviruses in the host genome. Moreover, global DNA hypomethylation is a key event for the initiation and progression of cancer [33]. In agreement, the strong association of HERV expression with DNA hypomethylation [34, 35] and with genome instability reflects the transcriptome changes [36].

Oncogenic mechanisms mentioned above involve HERVs as regulators of cell gene expression, but HERVs could also exert a direct action through own proteins. The env protein of HERV-K could contribute to tumorigenesis inducing cell-cell fusion as suggested by studies in melanoma [37], while syncytin-1 seems to be involved in fusogenic events in endometrial carcinoma [38] and in breast cancer [39].

In pancreatic cancer has been also demonstrated that HERV-K (HML-2) Env protein plays a role in cell proliferation and tumorigenesis, as well metastasis formation, by regulating KRAS through hyperactivation of the RAS/MEK/ERK pathway [31].

Another mechanism by which HERVs could contribute to tumorigenesis regards the promotion of the immune escape, as in the case of transmembrane env protein of HERV-H that possesses immunosuppressive properties. [40]. Moreover, the interference of env of HERV-H improved immune responses in vitro and in vivo accompanied by tumor regression [41].

To the best of our knowledge, this is the first study of HERV-R *pol* mRNA expression in pediatric leukemia showing that this molecule is overexpressed in the BM cells of patients compared with healthy subjects. In this study, we found a relative overexpression of the endogenous retrovirus HERV-R in the BM cells from the preponderance of leukemia samples analyzed. After considering the different mechanisms potentially involving HERVs in carcinogenesis, we suggest that overexpression of HERVs might participate in leukemogenesis. Furthermore, precise and larger quantitative study is needed for a possible application of the HERVs *pol* gene to clinical use such as leukemia marker.

Although the functional associations have not been yet completely clarified, a mounting body of evidence allows to highlight the HERVs as potential biomarkers for some complex diseases and provide an adequate evidence that HERV reactivation, even if not the direct cause of the disease, acts mostly as triggering factor [42]. Moreover, HERV expression studies could be supplemented by tests such as Western blot or immune assays using anti-HERV-P or R antibody to support the above results. More studies are warranted to evaluate the potential impact of HERVs *pol* expression on leukemia patients and its role in the regulation of signaling pathways involved in lymphoblastic leukemogenesis.

Author contributions P.M., I.G., C.C., and V.D. performed the analysis and developed the first draft of the manuscript; I.B. and M.B. assisted in the writing and editing of the manuscript; K.M helped edit the manuscript; and F.F. and M.B. wrote the manuscript. All authors provided critical revisions, gave final approval, and agreed to be accountable for the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Sverdlov ED (2000) Retroviruses and primate evolution. Bioessays 22:161–171
2. Bannert N, Kurth R (2006) The evolutionary dynamics of human endogenous retroviral families. Annu Rev Genomics Hum Genet 7: 149–173
3. Subramanian R, Wildschutte J, Russo C et al (2011) Identification, characterization, and comparative genomic distribution of the HERV-K(HML-2) group of human endogenous retroviruses. Retrovirology 8:90
4. Gotzinger N, Sauter M, Roemer K et al (1996) Regulation of human endogenous retrovirus-K gag expression in teratocarcinoma cell lines and human tumours. J Gen Virol 77:2983–2990
5. Katoh I, Kurata SI (2013) Association of endogenous retroviruses and long terminal repeats with human disorders. Front Oncol 3:234
6. Hohn O, Hanke K, Bannert N (2013) HERV-K (HML-2), the best preserved family of HERVs: endogenization, expression, and implications in health and disease. Front Oncol 3:246
7. Ruprecht K, Mayer J, Sauter M et al (2008) Endogenous retroviruses and cancer. Cell Mol Life Sci 6(5):3366–3382
8. Weiss RA (2006) The discovery of endogenous retroviruses. Retrovirology 3:67
9. Depil S, Roche C, Dussart P, Prin L (2002) Expression of a human endogenous retrovirus, HERV-K, in the blood cells of leukemia patients. Leukemia 16:254–259
10. Iwabuchi H, Kakihara T, Kobayashi T, Imai C, Tanaka A, Uchiyama M, Fakuda T (2004) A gene homologous to human endogenous retrovirus overexpressed in childhood acute lymphoblastic leukemia. Leuk Lymphoma 45:2303–2306
11. Januszkiewicz-Lewandowska D, Nowicka K, Rembowska J, Fichna M, Żurawek M, Derwich K, Nowak J (2013) Env gene expression of human endogenous retrovirus-K and human endogenous retrovirus-W in childhood acute leukemia cells. Acta Haematol 129:232–237. https://doi.org/10.1159/000345407
12. Bergallo M, Montanari P, Mareschi K, Merlino C, Berger M, Bini I, Daprà V, Galliano I, Fagioli F (2017) Expression of the pol gene of human endogenous retroviruses HERV-K and -W in leukemia

patients. Arch Virol 162(12):3639–3644. https://doi.org/10.1007/s00705-017-3526-7
13. Ahn K, Kim HS (2009) Structural and quantitative expression analyses of HERV gene in human tissues. Mol Cell 28:99–103
14. Yi JM, Kim HM, Kim HS (2004) Expression of the human endogenous retrovirus HERV-W family in various human tissues and cancer cells. J Gen Virol 85:1203–1210
15. Fischer S, Echeverría N, Moratorio G, Landoni AI, Dighiero G, Cristina J, Oppezzo P, Moreno P (2014) Human endogenous retrovirus np9 gene is over expressed in chronic lymphocytic leukemia patients. Leuk Res Rep 25:70–72. https://doi.org/10.1016/j.lrr.2014.06.005
16. Andersson AC, Venables PJ, Tonjes RR, Scherer J, Eriksson L, Larsson E (2002) Developmental expression of HERV-R (ERV3) and HERV-K in human tissue. Virology 297:220–225
17. Antony JM, Ellestad KK, Hammond R et al (2007) The human endogenous retrovirus envelope glycoprotein, syncytin-1, regulates neuroinflammation and its receptor expression in multiple sclerosis: a role for endoplasmic reticulum chaperones in astrocytes. J Immunol 179:1210–1224
18. Dulmage BO, Feng H, Mirvish E et al (2015) Black cat in a dark room: absence of a directly oncogenic virus does not eliminate the role of an infectious agent in CTCL pathogenesis. Br J Dermatol 172:1449–1451
19. Herbst H, Sauter M, Mueller-Lantzsch N (1996) Expression of human endogenousretrovirus K elements in germ cell and trophoblastic tumors. Am J Pathol 149:1727–1735
20. Herbst H, Sauter M, Kühler-Obbarius C et al (1998) Human endogenous retrovirus (HERV)-K transcripts in germ cell and trophoblastic tumours. APMIS 106:216–220
21. Herbst H, Kühler-Obbarius C, Lauke H et al (1999) Human endogenous retrovirus (HERV)-K transcripts in gonadoblastomas and gonadoblastoma-derived germ cell tumours. Virchows Arch 434:11–15
22. Benešová M, Trejbalová K, Kovářová D et al (2017) DNA hypomethylation and aberrant expression of the human endogenous retrovirus ERVWE1/syncytin-1 in seminomas. Retrovirology 14(20). https://doi.org/10.1186/s12977-017-0342-9
23. Rhyu DW, Kang YJ, Ock MS et al (2014) Expression of human endogenous retrovirus env genes in the blood of breast cancer patients. Int J Mol Sci 15:9173–9183. https://doi.org/10.3390/ijms15069173
24. Goering W, Schmitt K, Dostert M et al (2015) Human endogenous retrovirus HERV-K(HML-2) activity in prostate cancer is dominated by a few loci. Prostate 75:1958–1971. https://doi.org/10.1002/pros.23095
25. Maliniemi P, Vincendeau M, Mayer J et al (2013) Expression of human endogenous retrovirus-w including syncytin-1 in cutaneous T-cell lymphoma. PLoS One 8(10):e76281. https://doi.org/10.1371/journal.pone.0076281
26. Fava P, Bergallo M, Astrua C et al (2016) Human endogenous retrovirus expression in primary cutaneous T-cell lymphomas. Dermatology 232:38–43. https://doi.org/10.1159/000438669
27. Wentzensen N, Wilz B, Findeisen P et al (2004) Identification of differentially expressed genes in colorectal adenoma compared to normal tissue by suppression subtractive hybridization. Int J Oncol 24:987–994
28. Liang Q, Xu Z, Xu R et al (2012) Expression patterns of non-coding spliced transcripts from human endogenous retrovirus HERV-H elements in colon cancer. PLoS One 7:e29950. https://doi.org/10.1371/journal.pone.0029950
29. Giebler M, Staege MS, Blauschmidt S et al (2018) Elevated HERV-K expression in soft tissue sarcoma is associated with worsened relapse-free survival. Front Microbiol 9:211. https://doi.org/10.3389/fmicb.2018.00211
30. Ma W, Hong Z, Liu H et al (2016) Human endogenous retroviruses-K (HML-2) expression is correlated with prognosis and progress of hepatocellular carcinoma. Biomed Res Int 2016:8201642. https://doi.org/10.1155/2016/8201642
31. Li M, Radvanyi L, Yin B et al (2017) Downregulation of human endogenous retrovirus type K (HERV-K) viral env RNA in pancreatic cancer cells decreases cell proliferation and tumor growth. Clin Cancer Res 23:5892–5911. https://doi.org/10.1158/1078-0432.CCR-17-0001
32. Boeke JD, Stoye JP (1997) Retrotransposons, endogenous retroviruses, and the evolution of retroelements. In: Coffin JM, Hughes SH, Varmus HE (eds) Retroviruses. Cold Spring Harbour Laboratory Press, New York, pp 343–435
33. Sandoval J, Esteller M (2012) Cancer epigenomics: beyond genomics. Curr Opin Genet Dev 22:50–55. https://doi.org/10.1016/j.gde.2012.02.008
34. Stengel S, Fiebig U, Kurth R et al (2010) Regulation of human endogenous retrovirus-K expression in melanomas by CpG methylation. Genes Chromosom Cancer 49(5):401–411. https://doi.org/10.1002/gcc.20751
35. Kreimer U, Schulz WA, Koch A et al (2013) HERV-K and LINE-1 DNA methylation and reexpression in urothelial carcinoma. Front Oncol 3:255. https://doi.org/10.3389/fonc.2013.00255
36. Romanish MT, Cohen CJ, Mager DL (2010) Potential mechanisms of endogenous retroviral-mediated genomic instability in human cancer. Semin Cancer Biol 20:246–253. https://doi.org/10.1016/j.semcancer.2010.05.005
37. Huang G, Li Z, Wan X et al (2013) Human endogenous retroviral K element encodes fusogenic activity in melanoma cells. J Carcinog 12. https://doi.org/10.4103/1477-3163.109032
38. Strick R, Ackermann S, Langbein M, Swiatek J et al (2007) Proliferation and cell-cell fusion of endometrial carcinoma are induced by the human endogenous retroviral syncytin-1 and regulated by TGF-beta. J Mol Med 85:23–38. https://doi.org/10.1007/s00109-006-0104-y
39. Bjerregaard B, Holck S, Christensen IJ et al (2006) Syncytin is involved in breast cancer-endothelial cell fusions. Cell Mol Life Sci 63:1906–1911. https://doi.org/10.1007/s00018-006-6201-9
40. Mangeney M, de Parseval N, Thomas G et al (2001) The full-length envelope of an HERV-H human endogenous retrovirus has immunosuppressive properties. J Gen Virol 82:2515–2518. https://doi.org/10.1099/0022-1317-82-10-2515
41. Kudo-Saito C, Yura M, Yamamoto R et al (2014) Induction of immunoregulatory CD271+ cells by metastatic tumor cells that express human endogenous retrovirus H. Cancer Res 74:1361–1370. https://doi.org/10.1158/0008-5472.CAN-13-1349
42. Matteucci C, Balestrieri E, Argaw-Denboba A et al (2018) Human endogenous retroviruses role in cancer cell stemness. Semin Cancer Biol 53:17–30. https://doi.org/10.1016/j.semcancer.2018.10.001